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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/763,824	SQUIRRELL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-162* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *See Continuation Sheet* is/are allowed.

6)☒ Claim(s) *106-124,127,128,131,132,135,136,139,140,151,152,155,156,159 and 160* is/are rejected.

7)☒ Claim(s) *143,144,147 and 148* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Disposition of Claims: Claims allowed are 125,126,129,130,133,134,137,138,141,142,145,146,149,150,153,154,157,158,161 and 162.

Continuation of Attachment(s) 6). Other: Copies of Forms PTO-892 to include reference titles.

DETAILED ACTION

Status of the Application

[1] Claims 106-162 are pending in the application.

[2] Applicant's amendment to the claims, filed on 8/31/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's amendment to the specification, filed on 8/31/07, is acknowledged.

[4] Receipt of a sequence listing in computer readable form (CRF), a paper copy thereof, a statement of their sameness, a statement that no new matter has been added to the specification by the paper copy of the sequence CRF, and an amendment directing the sequence listing into the specification, all filed on 8/31/07, is acknowledged.

[5] Applicant's arguments filed on 8/31/07 have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[6] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Interview Request

[7] Applicant's request for an interview in the instant remarks at p. 9, top is acknowledged. In a telephone conversation with Mr. B.J. Sadoff on 11/19/07, the examiner informed Mr. Sadoff that a new obviousness rejection under 35 U.S.C. 103(a)

would be raised in a non-final Office action based on a newly found prior art reference, Thompson et al. (*J. Biol. Chem.* 272:18766-18771, 1997), that is not of record in the application file. Mr. Sadoff requested that the examiner provide a copy of the reference, which was provided electronically via e-mail. The examiner also informed Mr. Sadoff of the confusing language used as noted in the rejection under 35 U.S.C. 112, second paragraph, as set forth below.

Updated Forms PTO-892

[8] Applicant requests that the examiner provide updated Forms PTO-892 including the titles of all cited non-patent literature references. In accordance with applicant's request, updated Forms PTO-892 are attached to the instant Office action including the titles of cited non-patent literature references.

Specification/Informalities

[9] The amendment filed on 8/31/07 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the description of "Xaa" in SEQ ID NO:39 being "Asp", which is the 3-letter abbreviation for aspartate. While the examiner can find support for the position 214 substitutions as disclosed at p. 7, third paragraph, the examiner can find no descriptive support in the application as

filed for aspartate at position 214 of SEQ ID NO:38. Applicant is invited to show support for the limitation at issue.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, Second Paragraph

[10] Claims 106-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 106 (claims 107-108, 112-120 dependent therefrom) and 109-111 are confusing in the recitation of (using claim 106 as an example) "no more than 29 amino acids...which are different from the amino acids described in SEQ ID NO:38. By this recitation it appears that the comparison is based on amino acid composition, *not amino acid sequence.* However, based upon applicant's instant remarks at p. 12, first paragraph, it would appear that applicant intends for the "no more than 29 amino acids...which are different" to be a comparison of the amino acid sequences of the variant form of SEQ ID NO:38 and SEQ ID NO:38. It is suggested that applicant clarify the meaning of the claims. In the interest of advancing prosecution, the examiner has interpreted the phrase, "no more than 29 amino acids...which are different" as meaning a comparison of the amino acid sequences of the variant form of SEQ ID NO:38 and SEQ ID NO:38.

Claim Rejections - 35 USC § 112, First Paragraph

[11] Claims 107 and 122 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

MPEP § 2163 states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

Claims 107 and 122 (in relevant part) limits "Xaa" in SEQ ID NO:38 to being "Asp", which is the 3-letter abbreviation for aspartate. While the examiner can find support for the position 214 substitutions as disclosed at p. 7, third paragraph of the specification, the examiner can find no descriptive support in the application as filed for aspartate at position 214 of SEQ ID NO:38. Applicant is invited to show support for the limitation at issue.

Double Patenting Rejection(s)

[12] The provisional obviousness-type double patenting rejection of claims 86-105 as being unpatentable over claims 1-4, 6-10, 14-19, 21, 24-26, and 29-37 of co-pending Application No. 10/111,723 is withdrawn in view of applicant's amendment to cancel the claims. The provisional rejection is herein applied to newly added claims 106-107, 109,

112-115, 118-120, 127, 131, 135, 139, 151, 155, and 159 as being unpatentable over claims 1-4, 6-10, 14-16, 18-19, 21, and 35-37 of co-pending Application No. 10/111,723 is withdrawn in view of applicant's amendment to cancel the claims. The provisional rejection is herein applied to newly added claims 106-107, 109, 112-115, 118-120, 127, 131, 135, 139, 151, 155, and 159 for the reasons of record, particularly that the specification of the co-pending '723 application supports an embodiment of claims 1-4, 6-10, 14-16, 18-19, 21, and 35-37 that would anticipate claims 106-107, 109, 112-115, 118-120, 127, 131, 135, 139, 151, 155, and 159 herein, *i.e.,* Example 12 at pp. 42-43 of the '723 disclosure, which teaches a 214C/354K/357F *P. pyralis* luciferase mutant. The provisional rejection was fully explained in a prior Office action.

RESPONSE TO ARGUMENT: Applicant argues the rejection is moot since the instant application has an earlier filing date than the co-pending '723 application. However, this is not found persuasive because this provisional rejection is not the only remaining rejection and the co-pending '723 application supports an embodiment of claims 1-4, 6-10, 14-16, 18-19, 21, and 35-37 that would anticipate claims 106-107, 109, 112-115, 118-120, 127, 131, 135, 139, 151, 155, and 159 herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[13] Claim(s) 106-108, 112-115, 118-123, 127, 131, 135, 139, 151, 155, and 159 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. (*J. Biol. Chem.* 272:18766-18771, 1997; "Thompson U") in view of Thompson et al. (*Gene* 103:171-177, 1991; "Thompson V"), Hirokawa et al. (US Patent 6,074,859; "Hirokawa") and Lowe et al. (US Patent 6,132,983; "Lowe").

The claims are drawn to proteins comprising SEQ ID NO:38 and variants thereof as encompassed by the claims, encoding nucleic acids, vectors comprising the nucleic acids, transformed host cells, bioluminescent assays using said proteins, and kits comprising said proteins. According to the instant remarks, SEQ ID NO:38 "is the same as SEQ ID NO:37 of the previous Sequence Listing except for the inclusion or 'Xaa' at position 214 and a definition of Xaa as any amino acid" (p. 10, bottom). It is of note that "Xaa" of SEQ ID NO:38 in the sequence listing filed on 8/31/07 is actually defined as "an amino acid other than Thr". According to the remarks filed on 2/21/06 at p. 8, SEQ ID NO:37 is the sequence of wild-type *Photinus pyralis* luciferase.

The reference of Thompson U teaches "Luciferase is highly susceptible to proteolysis *in vitro* and has a very short half-life *in vivo*...For different applications, this can create either an advantage or disadvantage...This paper describes new forms of luciferase with altered luminescent properties that may allow some of these problems to be circumvented" (p. 18766, column 2, bottom). Thompson U teaches regions of amino acid sequence 206-220 and 329-341 of *Photinus pyralis* luciferase were found to be

protease sensitive "and because the region around 206-220 had high homology with other luciferases...this region was selected for mutagenesis experiments intended to determine which of its amino acids were essential for activity" (p. 18766, abstract). The reference of Thompson U shows that within the region of amino acids 206-220 of *P. pyralis* luciferase, there are four protease cleavage sites, including a trypsin cleavage site between amino acids Arg213 and Thr214 (p. 18768, Figure 2). Identifying amino acids 206-220 as being a region within *P. pyralis* luciferase that is sensitive to proteolysis and substitution of amino acids within this region, namely amino acids 194 and 196-203, with Ala or other amino acids (p. 18767, column 2 to p. 18768, column 1), "was successful in allowing us to generate functionally interesting mutations" (p. 18769 (column 2, middle), including alteration to substrate affinity, light emission, and pH optima (p. 18769, Figure 5 and Table I, p. 18770, Figures 6 and 7), noting that these studies "not only provide insight into how luciferase carries out its luminescent reaction but also provides an improved reporter system (p. 18770, column 2). The method of mutation according to Thompson U involves replacing the codon at the desired position within a vector comprising a nucleic acid encoding wild-type *P. pyralis* luciferase, transforming a bacterial host with the mutant vector, recombinantly expressing the encoded protein, and optionally measuring by luciferase assay the luciferase activity of the resulting mutant luciferase (p. 18767, column 1).

Although Thompson U teaches that the region of amino acids 206-220 of *P. pyralis* luciferase were selected for mutagenesis studies, the reference does not specifically teach mutation at position 214 of *P. pyralis* luciferase.

The reference of Thompson V teaches that stability of a reporter protein is "critical for proper interpretation of results" and acknowledges problems in using luciferase as a reporter, namely stability and half-life of the protein (p. 171, abstract and column 2). In order to circumvent these problems, Thompson V suggests the use of luciferin analogs, which are proposed to alter conformation of the luciferase polypeptide and thus increasing stability and half-life (p. 175, columns 1-2).

At the time of the invention, it was known in the prior art that *P. pyralis* luciferase mutants with substitution at position 215 or 217 have improved properties relative to wild-type *P. pyralis* luciferase. For example, the reference of Lowe teaches an A215L mutant of *P. pyralis* luciferase has increased stability relative to wild-type *P. pyralis* luciferase (*e.g.*, Figures 14-15). Similarly, the reference of Hirokawa teaches a position 217 mutant of *P. pyralis* luciferase, which has increased stability relative to wild-type *P. pyralis* luciferase (*e.g.*, column 1, line 35 to column 2, line 4; column 4, lines 1-2).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Thompson U, Lowe, and Hirokawa to mutate wild-type *P. pyralis* luciferase at position 214 to alanine by the method of Thompson U, Lowe, or Hirokawa and test the resulting mutant by the methods according to Thompson U. One would have been motivated to do this because: Thompson U specifically identifies amino acids 206-220 as a region for mutation; Thompson U specifically teaches replacing amino acids within this region with alanine; Thompson U, Lowe, and Hirokawa each demonstrates that amino acid mutation within this region produces mutant *P. pyralis* luciferase polypeptides with improved stability relative to wild-type *P. pyralis;* and

the use of a stabilized mutant luciferase would increase half-life and stability without requiring luciferin analogs. One would have a reasonable expectation of success to practice the method of mutating wild-type *P. pyralis* luciferase at position 214 to alanine by the method of Thompson U, Lowe, or Hirokawa and test the resulting mutant by the methods according to Thompson U because of the results of Thompson U, Lowe, and Hirokawa.

It is acknowledged that the prior art is silent with regard to the effects of mutating *P. pyralis* luciferase at position 214. However, according to MPEP 2112, "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.'" Thus, although the prior art is silent to the effects of mutating *P. pyralis* luciferase at position 214, a *P. pyralis* luciferase with mutation at position 214 would necessarily have luciferase activity and increased thermostability as compared to wild-type *P. pyralis* luciferase.

Therefore, claims 106-108, 112-115, 118, 121-123, 127, 131, 135, 139, and 151, drawn to a polypeptide, nucleic acid, vector, cell, and method as described above would have been obvious to one of ordinary skill in the art.

Regarding claims drawn to kits, *i.e.,* claims 119-120, 155, and 159, it is noted that the examiner can find no specific definition of the term "kit" in the specification and has broadly, but reasonably interpreted the term as encompassing any container suitable for holding the recited polypeptide. Although the reference of Thompson U does

not specifically teach a "kit" containing a polypeptide, the reference of Thompson U does suggest aliquoting the protein for storage and using aliquots of the protein in luciferase assays including contacting the luciferase with luciferin (p. 18767, column 1, middle to bottom). As such, it would have been obvious at the time of the invention to store a *P. pyralis* luciferase with mutation at position 214 in a container, optionally in the presence of luciferin. One would have been motivated to do this in order to preserve the polypeptide or conduct a luciferase assay in accordance with the teachings of Thompson U. One would have a reasonable expectation of success to store a *P. pyralis* luciferase with mutation at position 214 in a container, optionally in the presence of luciferin because of the results of Thompson U, Lowe, and Hirokawa. Therefore, claims 119-120, 155, and 159, drawn to kits as described above would have been obvious to one of ordinary skill in the art.

[14] Claim(s) 109, 124, 128, 132, 136, 140, 152, 156, and 160 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson U in view of Hirokawa and Lowe as applied to claims 106-108, 112-115, 118-123, 127, 131, 135, 139, 151, 155, and 159 above, and further in view of additional teachings of Thompson U and Lowe. The claims are drawn to proteins comprising SEQ ID NO:40 and variants thereof as encompassed by the claims, encoding nucleic acids, vectors comprising the nucleic acids, transformed host cells, bioluminescent assays using said proteins, and kits comprising said proteins. According to the instant remarks at pp. 10-11, SEQ ID NO:40 is SEQ ID NO:37 with "Xaa" at position 214 defined as alanine and "Xaa" at position 354 defined as lysine.

The teachings of Thompson U, Lowe, and Hirokawa are described above. The combination fails to teach a *Photinus pyralis* luciferase mutated at positions 214 and 354 with alanine and lysine, respectively.

Thompson U additionally teaches that crude extract of the recombinant protein "slowly lost activity on storage" and "To prevent this", additional steps were required to purify the recombinant protein to prevent loss of activity and that even this preparation exhibited a loss of activity "over several days" of storage (p. 18767, column 1, middle).

Lowe additionally teaches *Photinus pyralis* luciferase mutated at position 354 with lysine, wherein the mutant has increased stability relative to wild-type *Photinus pyralis* luciferase (*e.g.,* Figures 14 and 15).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Thompson U, Lowe, and Hirokawa to use the *Photinus pyralis* luciferase position 354 mutant as the "parent" polypeptide (in place of wild-type *Photinus pyralis* luciferase) for mutation at position 214 by the method of Thompson U, Lowe, or Hirokawa and test the resulting mutant by the methods according to Thompson U. One would have been motivated to use the *Photinus pyralis* luciferase position 354 mutant as the "parent" polypeptide since the *Photinus pyralis* luciferase position 354 mutant has increased stability and would be expected to maintain activity longer relative to wild-type *Photinus pyralis* luciferase over time. One would have a reasonable expectation of success to use the *Photinus pyralis* luciferase position 354 mutant as the "parent" polypeptide (in place of wild-type *Photinus pyralis* luciferase) for mutation at position 214 because of the results of Thompson U, Lowe, and Hirokawa.

It is acknowledged that the prior art is silent with regard to the effects of mutating *P. pyralis* luciferase at positions 214 and 354. However, according to MPEP 2112, "The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "'The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness.'" Thus, although the prior art is silent to the effects of mutating *P. pyralis* luciferase at positions 214 and 354, a *P. pyralis* luciferase with mutations at positions 214 and 354 would necessarily have luciferase activity and increased thermostability as compared to wild-type *P. pyralis* luciferase.

Therefore, claims, 109, 124, 128, 132, 136, 140, and 152, drawn to a polypeptide, nucleic acid, vector, cell, and method as described above would have been obvious to one of ordinary skill in the art.

Regarding claims drawn to kits, *i.e.,* claims 156 and 160, it is noted that the examiner can find no specific definition of the term "kit" in the specification and has broadly, but reasonably interpreted the term as encompassing any container suitable for holding the recited polypeptide. Although the reference of Thompson U does not specifically teach a "kit" containing a polypeptide, the reference of Thompson U does suggest aliquoting the protein for storage and using aliquots of the protein in luciferase assays including contacting the luciferase with luciferin (p. 18767, column 1, middle to bottom). As such, it would have been obvious at the time of the invention to store a *P. pyralis* luciferase with mutation at position 214 in a container, optionally in the presence of luciferin. One would have been motivated to do this in order to preserve the

polypeptide or conduct a luciferase assay in accordance with the teachings of Thompson U. One would have a reasonable expectation of success to store a *P. pyralis* luciferase with mutations at positions 214 and 354 in a container, optionally in the presence of luciferin because of the results of Thompson U, Lowe, and Hirokawa. Therefore, claims 156 and 160, drawn to kits as described above would have been obvious to one of ordinary skill in the art.

Conclusion

[15] Status of the claims:

Claims 106-162 are pending.

Claims 106-124, 127-128, 131-132, 135-136, 139-140, 151-152, 155-156, and 159-160 are rejected.

Claims 125-126, 129-130, 133-134, 137-138, 141-142, 145-146, 149-150, 153-154, 157-158, and 161-162 would appear to be in condition for allowance.

Claims 143-144 and 147-148 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656